THE ROLE OF EPA CLINICAL RESEARCH IN SETTING AIR QUALITY STANDARDS

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Role of Clinical Research in Air Quality Standards?

- **Ethical Considerations**
- **Scientific Value**

What Are Controlled Human Exposure Studies?

- **Volunteers**
- **Controlled Pollutant Conditions**
- **Randomization to Treatment**
- **Measurement of Health Effect**
- **Compare Pollutant Effects with Air Control**

"Effective" and "Optimal" Standards

- **High Probability of Meeting Requirements of the Law**
- **Not Unnecessarily Restrictive**

Health Information Needed to Identify an Optimal Standard

- **Does Pollutant Cause Effect?**
- **Accurate Estimates of Human Health Effects in Population**
  - **Existing Conditions**
  - **Set of Alternate Regulatory Scenarios**
- **Uncertainty of Above Estimates**

Why Does Uncertainty Matter?

More Uncertainty in Health Data Decreases the Probability of Identifying an Optimal Standard

Sources of Uncertainty in Health Data

- **Interspecies Extrapolation**
- **Individual Variability**
- **Bias in Epidemiology Studies**
- **What is Adverse?**
- **Limited Amount of Data**

How Can Clinical Research Improve Accuracy and Add Precision to Estimates of the Health Effects of Air Pollutants in Humans?

Strengths of Clinical Studies

- **Randomization**
  - **Establish Causality**
  - **Unbiased estimates of effect**
- **Species of Interest**
- **Control and Accurately Measure Exposure**

Limitations of Clinical Studies (Ethical)

- **Pollutants with Limited, Acute, Reversible Effects**
- **Susceptible Populations**
- **Limited Health Endpoints**

Limitations of Clinical Studies (Logistic)

- **Small Sample Sizes**
  - **Rare Outcomes Difficult to Study**
  - **Interactions Difficult to Study**
- **Short Duration**
- **Volunteers May Not Be Representative of Population**
- **Can't Totally Reproduce Ambient Environment**

Contributions to Accuracy and Precision by Clinical Studies

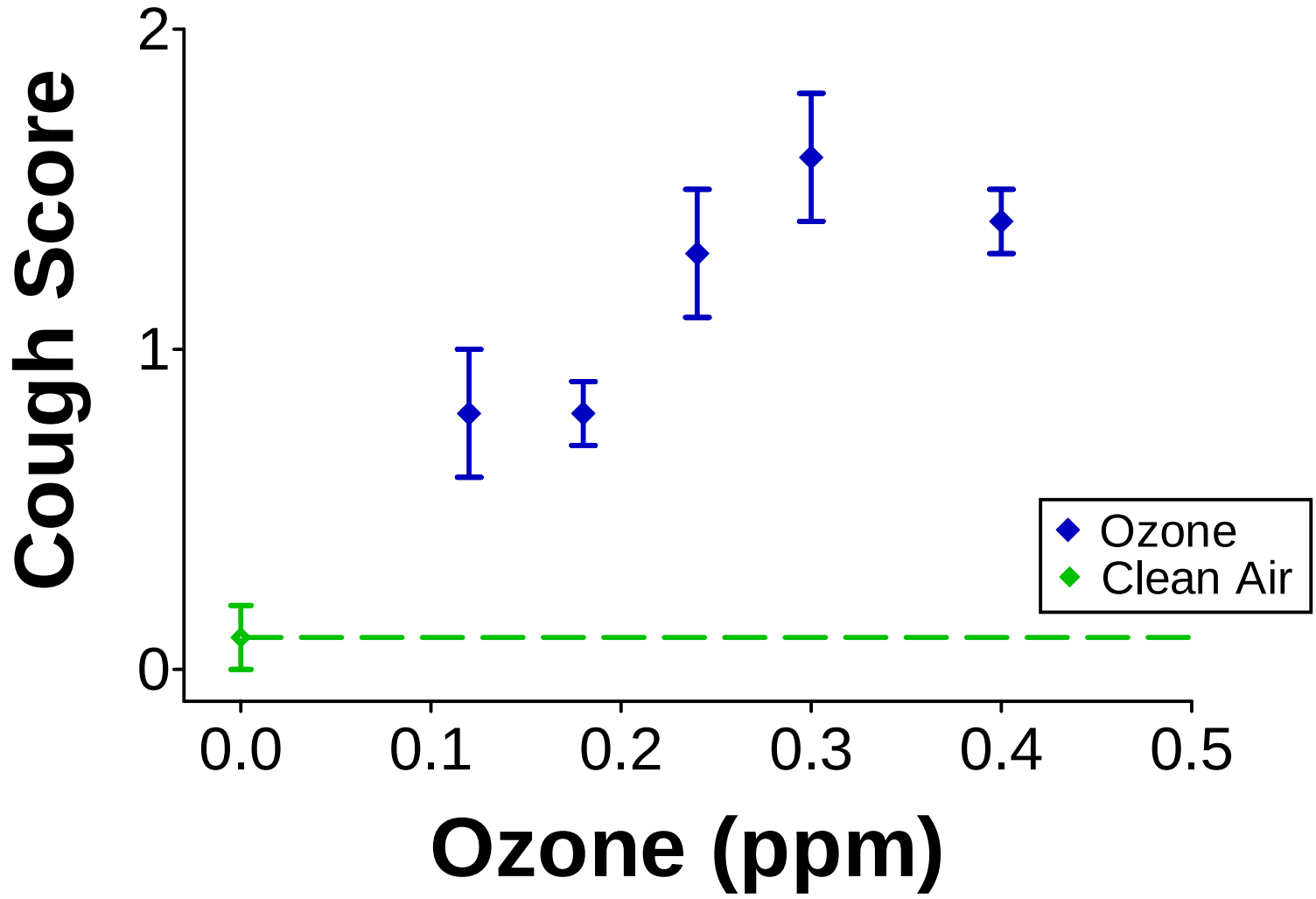
- **Ozone and Eye Irritation**
- **Ozone and Asthma Attacks**
- **Chlorine and Nasal Lesions**
- **NAAQS for Ozone**

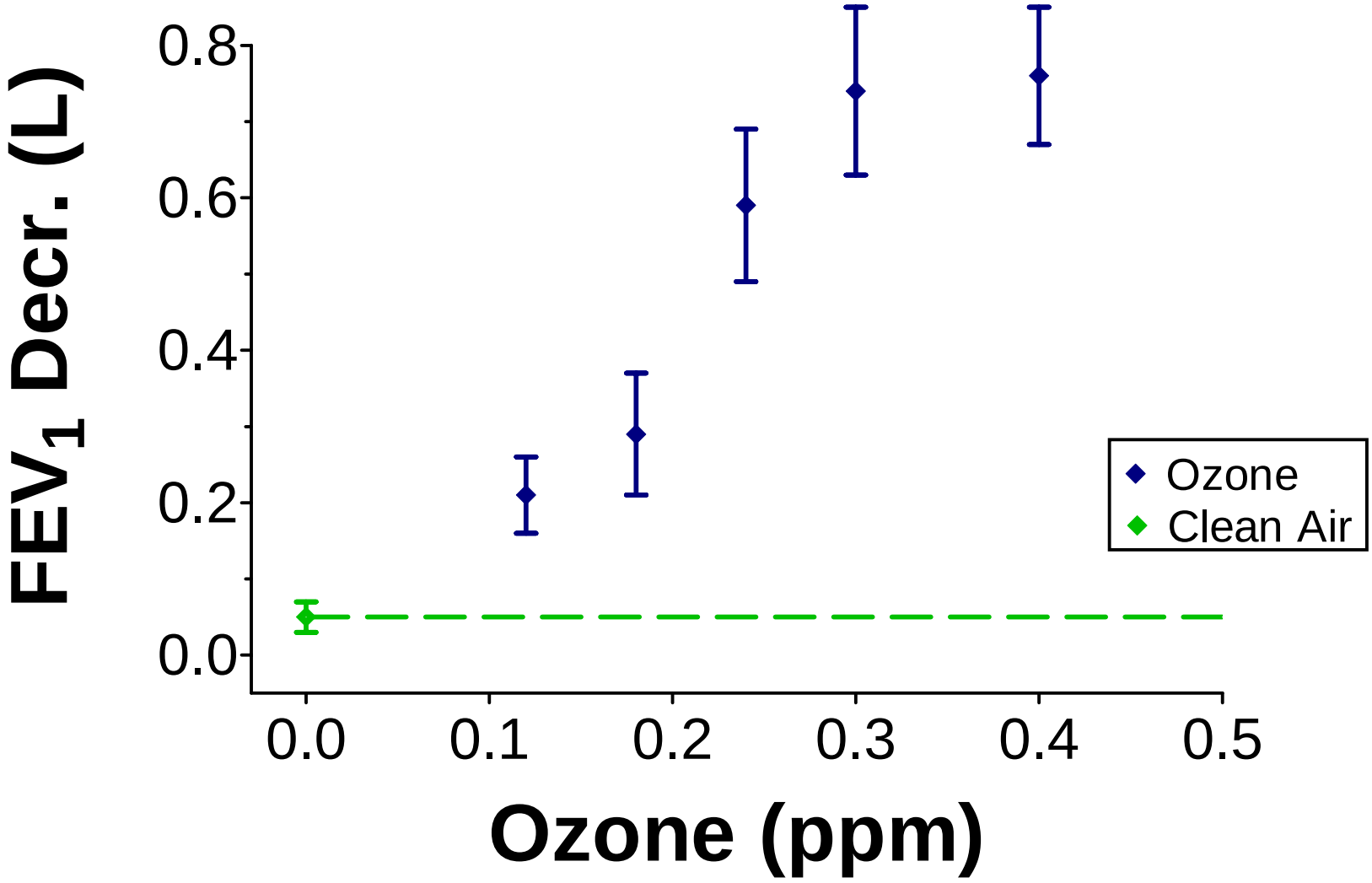
NAAQS for Ozone

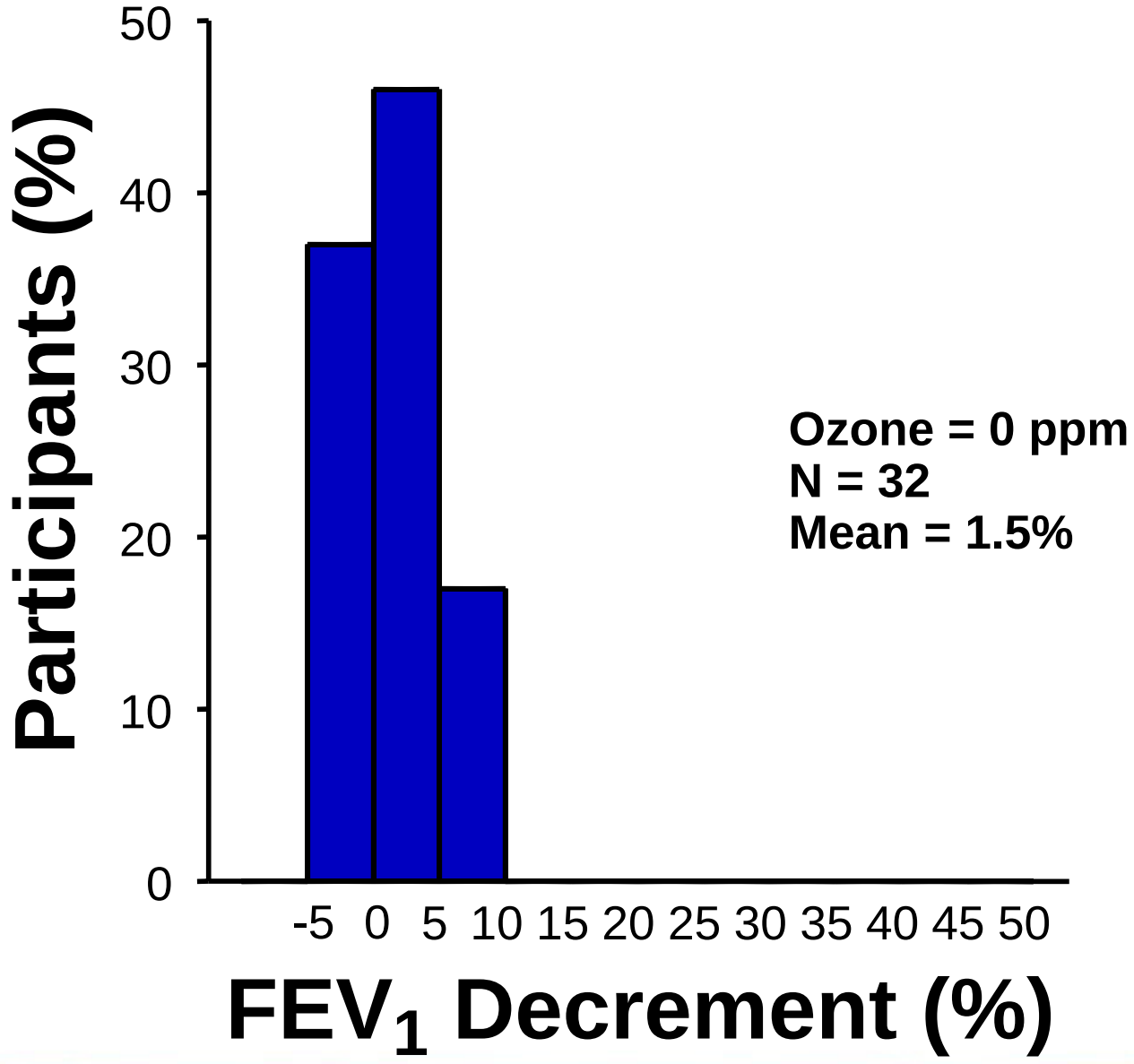
- **1971- 1 hr 0.08 ppm oxidants**
- **1979 – 1 hr 0.12 ppm ozone**
- **1997 – 8 hr 0.08 ppm ozone**

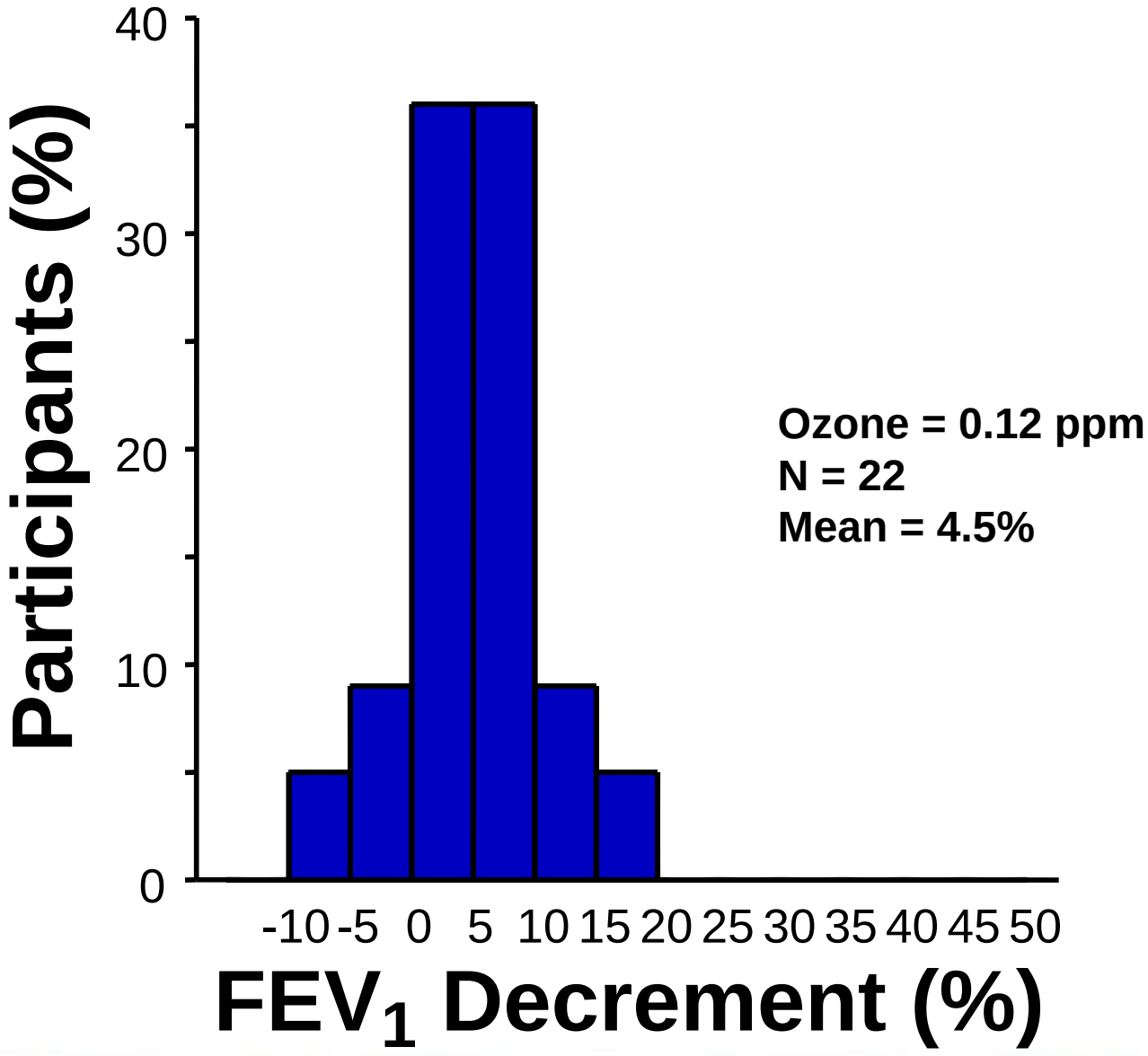
2-hr Ozone Exposures

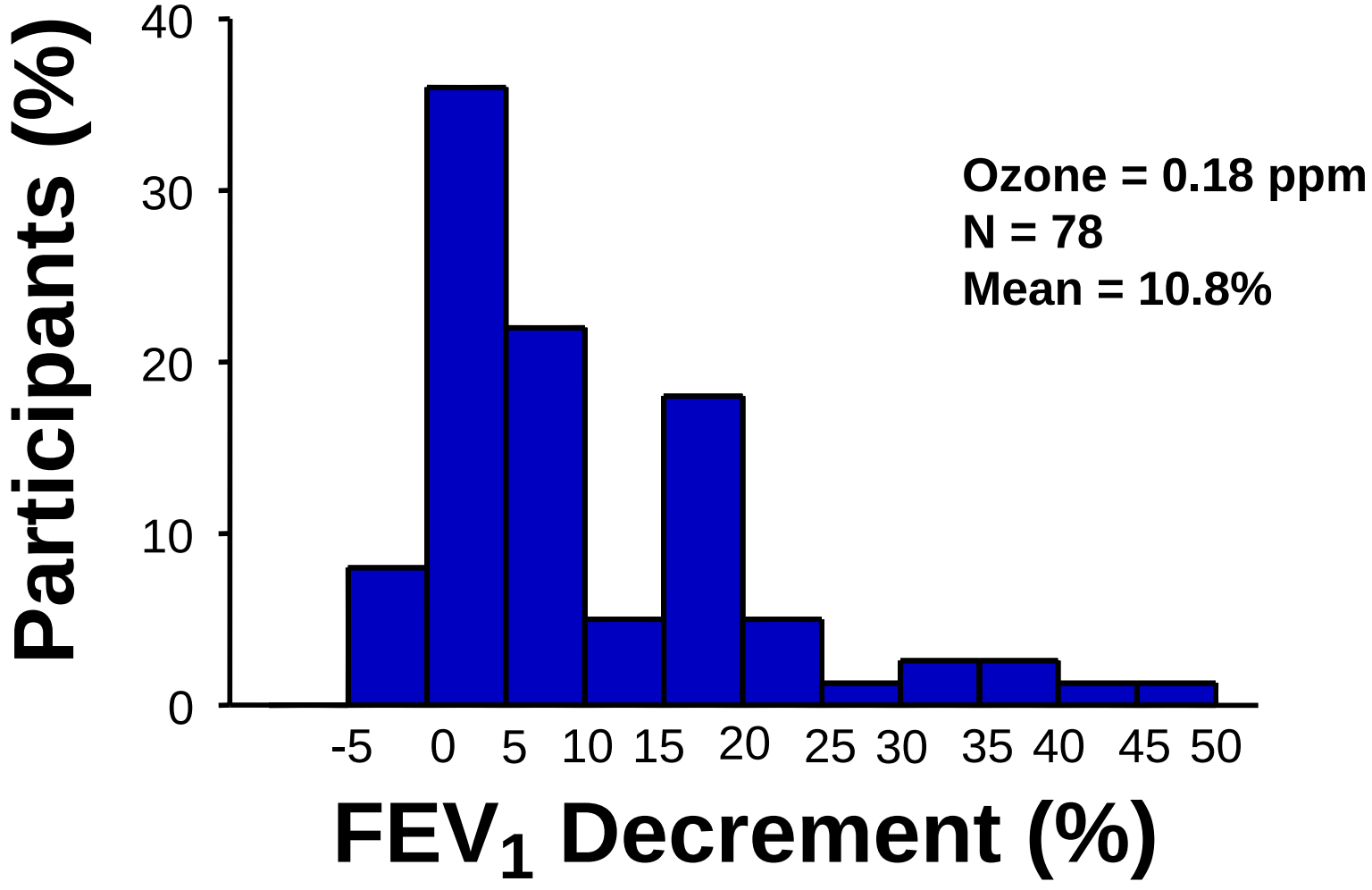
- **Healthy, Young Adults**
- **0.0, 0.12, 0.18, 0.30, 0.40 ppm Ozone**
- **Alternate Rest/Heavy Ex.**
- **FEV_1 /Symptoms**

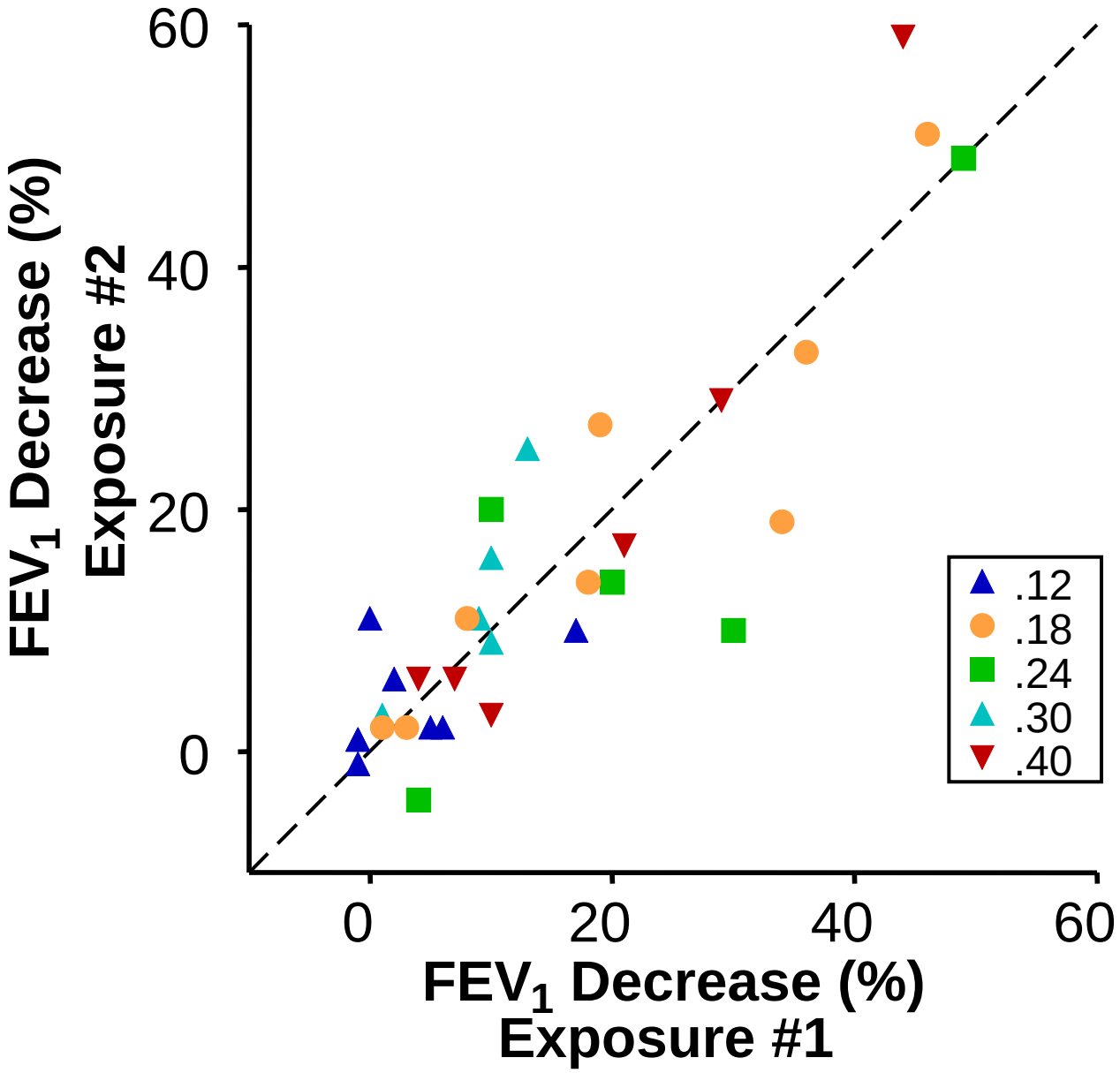

Cough Score
2
1
0
0.0
0.1
0.2
0.3
0.4
0.5
Ozone (ppm)
Ozone
Clean Air

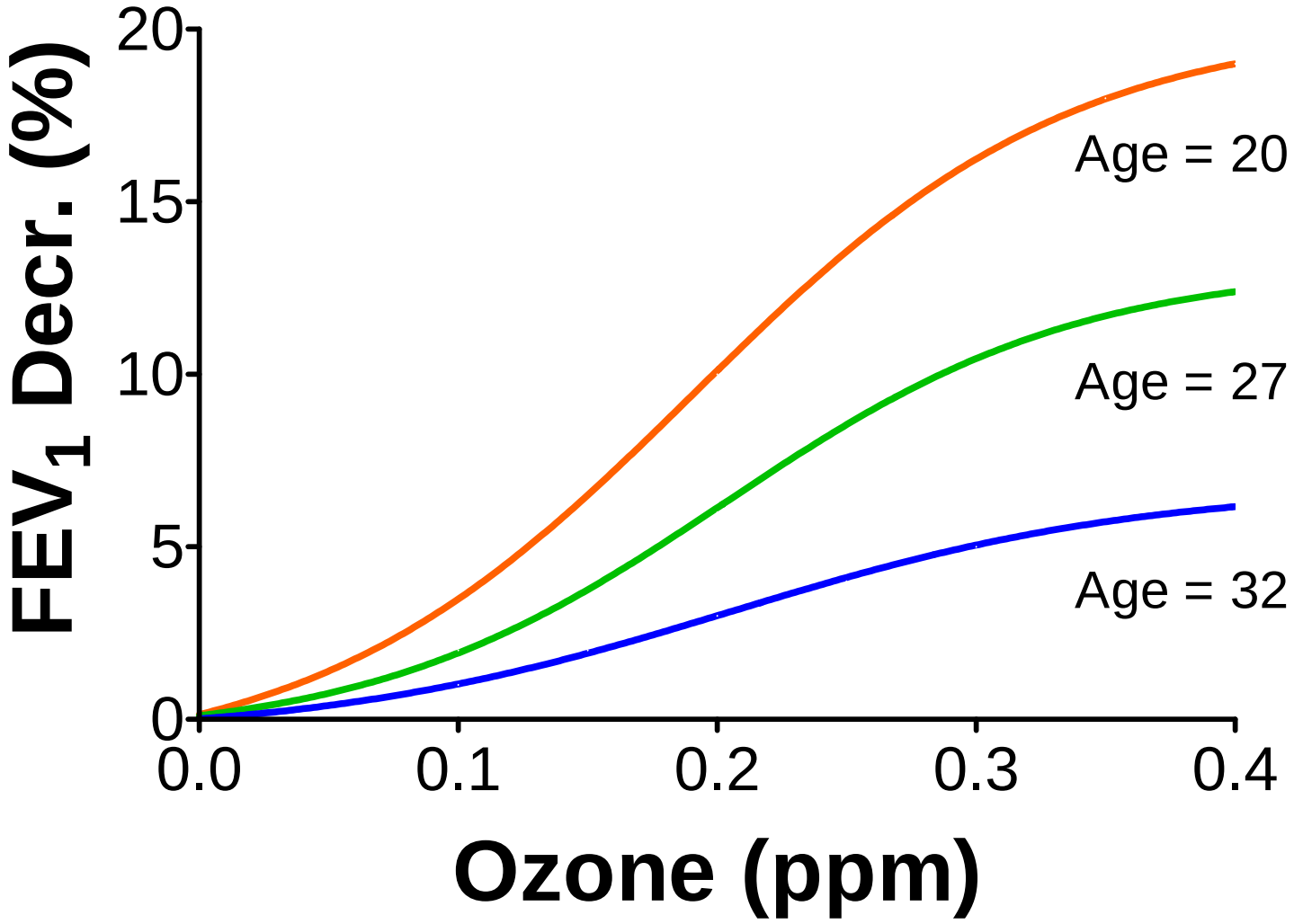

FEV1 Decr. (L)
0.8
0.6
0.4
0.2
0.0
0.0
0.1
0.2
0.3
0.4
0.5
Ozone (ppm)
Ozone
Clean Air


Participants (%)
50
40
30
20
10
0
-5 0 5 10 15 20 25 30 35 40 45 50
FEV1 Decrement (%)
Ozone = 0 ppm
N = 32
Mean = 1.5%


Participants (%)
40
30
20
10
0
-10 -5 0 5 10 15 20 25 30 35 40 45 50
FEV1 Decrement (%)
Ozone = 0.12 ppm
N = 22
Mean = 4.5%

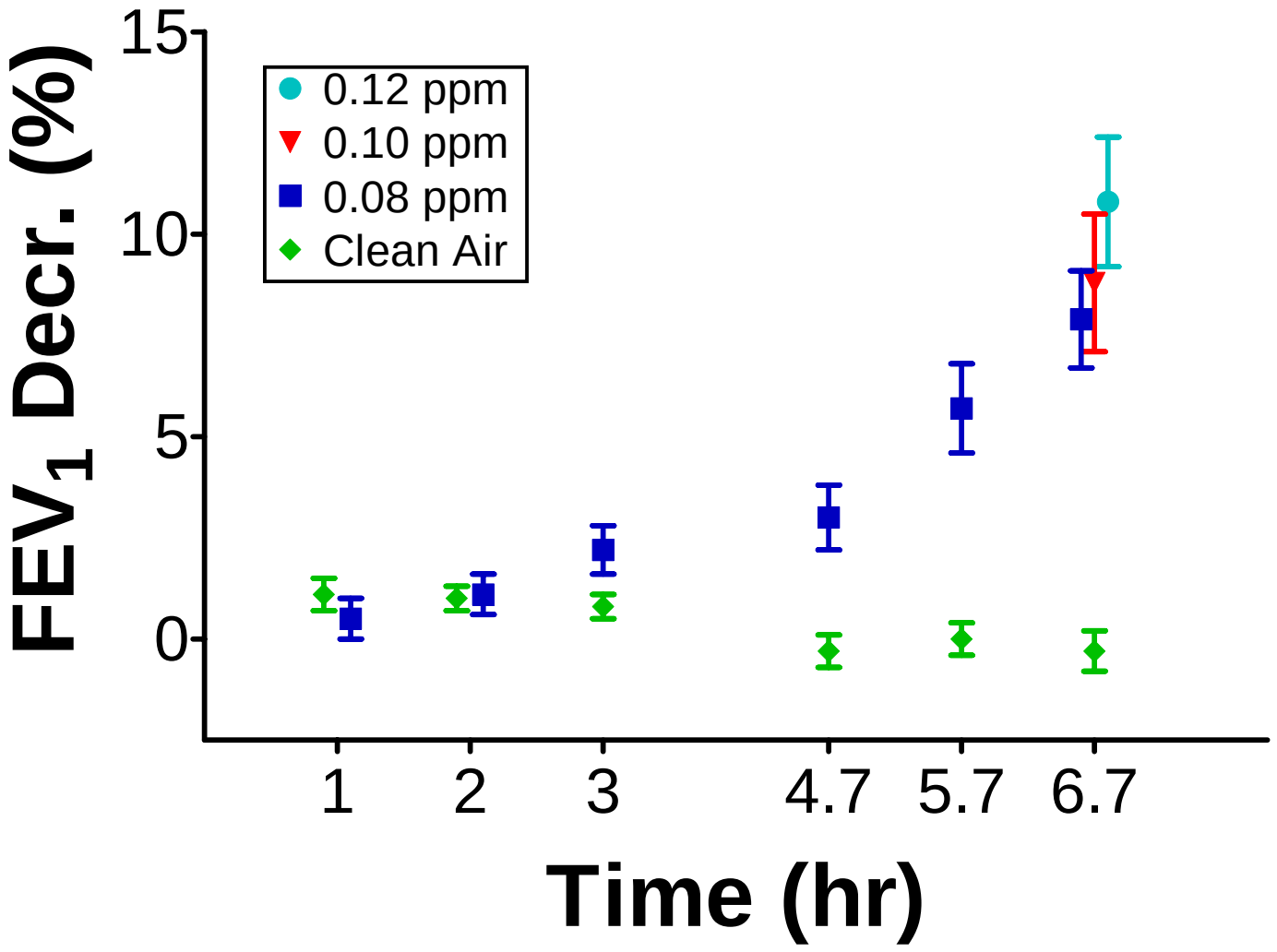

Participants (%)
40
30
20
10
0
-5
0
5
10
15
20
25
30
35
40
45
50
FEV1 Decrement (%)
Ozone = 0.18 ppm
N = 78
Mean = 10.8%

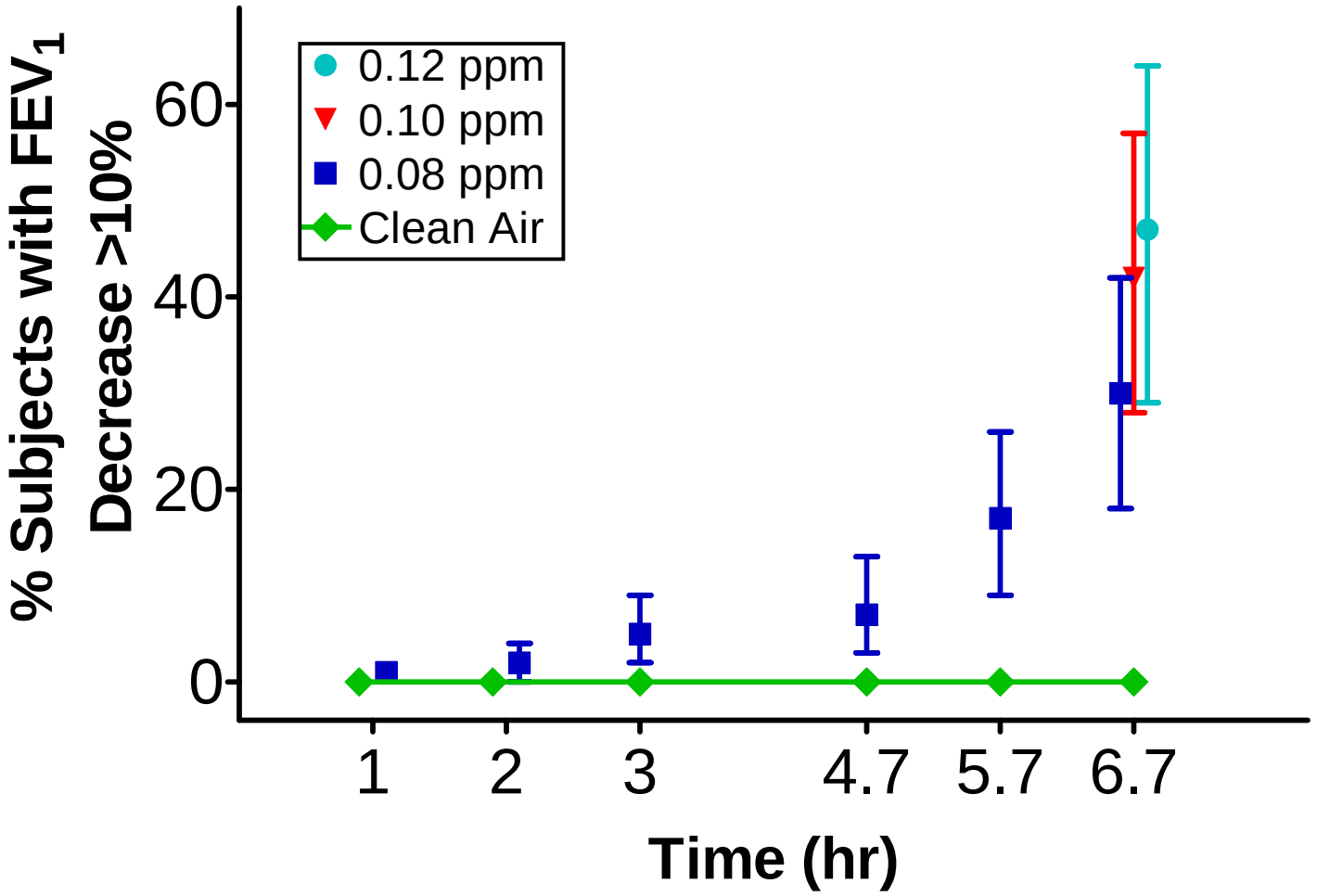

60
40
20
0
0
20
40
60
FEV1 Decrease (%)
Exposure #2
FEV1 Decrease (%)
Exposure #1
.12
.18
.24
.30
.40


FEV1 Decr. (%)
20
15
10
5
0
0.0
0.1
0.2
0.3
0.4
Ozone (ppm)
Age = 20
Age = 27
Age = 32

6.7-hr Ozone Exposures

- **Healthy, Young Adults**
- **0.0, 0.08, 0.10, 0.12 ppm Ozone**
- **Alternate Moderate Ex./Rest**
- **FEV_1 /Symptoms**


15
10
5
0
FEV1 Decr. (%)
0.12 ppm
0.10 ppm
0.08 ppm
Clean Air
1
2
3
4.7
5.7
6.7
Time (hr)


% Subjects with FEV1 Decrease >10%
0.12 ppm
0.10 ppm
0.08 ppm
Clean Air
60
40
20
0
1
2
3
4.7
5.7
6.7
Time (hr)

Health Information Needed to Identify an Optimal Standard

- **Does Pollutant Cause Effect?**
- **Accurate Estimates of Human Health Effects in Population**
  - **Existing Conditions**
  - **Set of Alternate Regulatory Scenarios**
- **Uncertainty of Above Estimates**

EPA Clinical Studies Support for 1-hr and 8 hr NAAQS for Ozone

- **Demonstrated Causality**
- **Accurate Estimates of Effect**
  - **Mean**
  - **Individual Variability**
  - **Sensitive Subpopulations**
  - **Exposure-Response Models**
- **Estimates of Precision**

CONCLUSIONS

- **In the right circumstances, clinical studies (CS) directly establish causality and provide accurate and precise estimates of effect.**
- **In less optimal circumstances, CS complement animal and epidemiology data decreasing uncertainty.**

CONCLUSIONS

- **Clinical studies usually increase the probability that an optimal standard will be identified.**
- **Clinical studies clearly have a role to play in standard setting.**